(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00271 A1

(51) International Patent Classification[7]: A61L 27/14, C08G 65/48, C08J 7/12, A61L 31/04

(21) International Application Number: PCT/GB01/02818

(22) International Filing Date: 22 June 2001 (22.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0015427.8 24 June 2000 (24.06.2000) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/00271 A1

(54) Title: BIO-COMPATIBLE POLYMERIC MATERIALS

(57) Abstract: A method of functionalising a polymer to produce a bio-compatible polymeric material which includes bio-compatible moieties and is for use in medical applications comprises, in preferred embodiments, the treatment of a polyaryletherketone/sulphone polymer (e.g. polyetherketone or polyetheretherketone) to functionalise phenyl moieties thereof at or adjacent a surface of the polymer whilst not functionalising corresponding phenyl moieties in the bulk of said polymer and associating bio-compatible moieties with said functionalised phenyl moieties so that said bio-compatible moieties are at or adjacent the surface of the polymer.

BIO-COMPATIBLE POLYMERIC MATERIALS

This invention relates to bio-compatible polymeric materials and particularly, although not exclusively, relates to a method of producing a bio-compatible polymeric material, such a material per se and the use of such a material in medical treatment, for example in a prosthesis.

Much research is being directed to the provision of materials to meet the growing need for prosthetic devices such as orthopaedic, dental or maxillofacial implants. For example, nearly half a million patients receive bone implants each year in the US with the majority being artificial hip and knee joints made from titanium or colbalt-chrome alloys. However, these materials are too stiff leading to bone resorption, loosening of the implant and, consequently, have lifetimes of less than 10 years. Additionally, medical devices or prostheses such as pacemakers, vascular grafts, stents, heart valves, catheters and dental implants that contact body tissues or fluids of living persons or animals have been developed and used clinically.

A major problem with medical devices such as those described is the susceptibility to foreign body reaction and possible rejection. Consequently, it is of great interest to the medical industry to develop materials from which medical devices can be made which are less prone to adverse biological reactions that typically accompany introduction of medical devices into humans or animals.

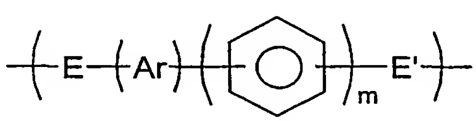
It is an object of the present invention to address the above described problems.

It is known to functionalise polymers with bio-compatible moieties. However, known functionalised polymers tend to have relatively low concentration of associated bio-compatible moieties.

It is an object of the present invention to address the abovedescribed problems.

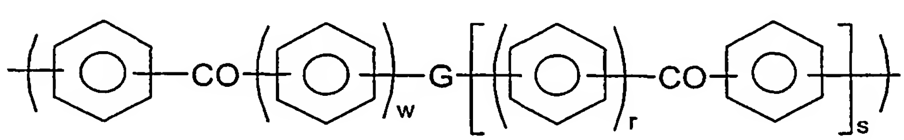
According to a first aspect of the invention, there is provided a method of functionalising a polymer to produce a bio-compatible polymeric material which includes bio-compatible moieties and is for use in medical applications, the method including the stages of:

(1) treating a polymer which has a moiety of formula



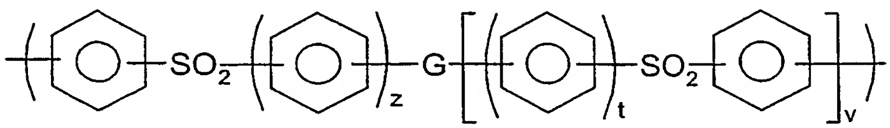
I

and/or a moiety of formula



II

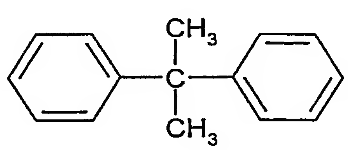
and/or a moiety of formula

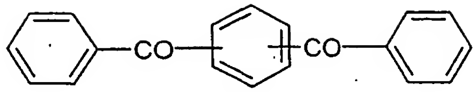


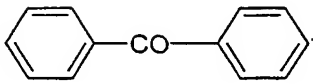
III

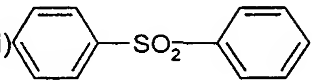
to functionalise aryl, especially phenyl, moieties in said polymer (hereinafter referred to as "functionalised aryl moieties") at or adjacent a surface of the polymer whilst not functionalising corresponding aryl moieties in the bulk of said polymer, wherein the phenyl moieties in units I, II, and III (prior to functionalisation) are independently optionally substituted and optionally cross-linked; and wherein m,r,s,t,v,w and z independently represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)*, (i)**,(i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties

(i)**



(i)* 

(i) 

(ii) 

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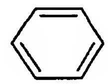
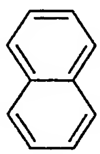
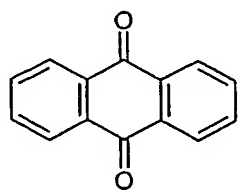
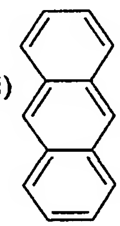
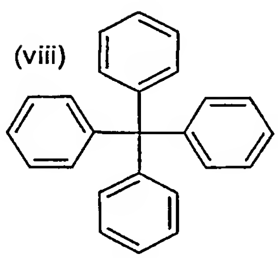
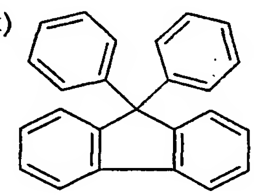
(iv) 

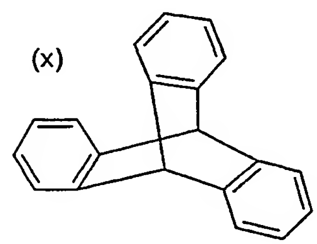
(v) 

(vi) 

(vii) 

(viii) 

(ix) 

(x) 

(2) associating bio-compatible moieties with said functionalised aryl moieties so that said bio-compatible moieties are at or adjacent the surface of the polymer.

Except where otherwise stated, throughout this specification, any alkyl, akenyl or alkynyl moiety suitably has up to 8, preferably up to 6, more preferably up to 4, especially up to 2, carbon atoms and may be of

straight chain or, where possible, of branched chain structure. Generally, methyl and ethyl are preferred alkyl groups and C_2 alkenyl and alkynyl groups are preferred.

Except where otherwise stated in this specification, optional substituents of an alkyl group may include halogen atoms, for example fluorine, chlorine, bromine and iodine atoms, and nitro, cyano, alkoxy, hydroxy, amino, alkylamino, sulphinyl, alkylsulphinyl, sulphonyl, alkylsulphonyl, amido, alkylamido, alkoxycarbonyl, haloalkoxycarbonyl and haloalkyl groups. Preferably, optionally substituted alkyl groups are unsubstituted.

In the scientific literature there is inconsistency in the use of descriptions such as "bio-compatible", "bio-active" and "bio-materials". In the context of the present specification, the term "bio-compatible" has generally been used to refer to a material which is compatible with use in medical applications, for example by not being toxic or otherwise harmful to living materials. It also encompasses materials which have a biological or physiological effect when associated with living materials.

"Bio-compatible moieties" referred to herein suitably refer to moieties which are compatible with use in medical applications, for example by not being toxic or otherwise harmful to living material. Such bio-compatible moieties may be arranged to bond (for example to form ionic or covalent bonds) or otherwise interact with materials present in human or animal bodies in order to improve their integration and acceptance by such bodies.

Preferably, said bio-compatible polymeric material produced in the method has improved or enhanced bio-compatibility compared to said polymer in the absence of bio-compatible moieties associated with functionalised aryl groups thereof.

Bio-compatible moieties suitably include moieties arranged to reduce adverse biological reactions when the bio-compatible polymeric material is introduced into (or otherwise associated with) a human or animal body. For example, adverse biological reactions associated with introduction into a human or animal body of said polymer having said bio-compatible moieties may be less compared to use of the same polymer but which does not include associated bio-compatible moieties.

A said bio-compatible moiety may be selected from an anticoagulant agent such as heparin and heparin sulfate, an antithrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defence agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein such as avidin, a glycoprotein, a globular protein, a structural protein, a membrane protein and a cell attachment protein, a peptide such as a glycopeptide, a structural peptide, a membrane peptide and a cell attachment peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent such as pencillin, ticarcillin, carbenicillin, ampicillin, oxacillian, cefazolin, bacitracin, cephalosporin, cephalothin, cefuroxime, cefoxitin,

norfloxacin, perfloxacin and sulfadiazine, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, biotin, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a nucleotide, a polynucleotide, a nucleoside, a lectin, a ligand and a dye (which acts as a biological ligand), a radioisotope, a chelated radioisotope, a chelated metal, a metal salt, a sulphonic acid or salt thereof, a steroid, a non-steroid, a non-steroidal anti-inflammatory, an analgesic, an anti-histamine, a receptor binding agent, a chemotherapeutic agent, a hydrophilic polymer (e.g. poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), ethylene oxide-propylene oxide block co-polymers, poly(N-vinyl-2-pyrrolidone) (PNVP), poly(2-hydroxyethyl methacrylate) (pHEMA), HEMA co-polymers, poly(vinyl alcohol) (PVA), polyacrylamide, its derivatives, poly(methyl methacrylate) (PMMA), suitably having a PEG chain on each of the side groups, polysiloxanes (e.g. polydimethylsiloxanes (PDMS)), ionic water-soluble polymers like poly(acrylic acid) (PAAc)) and a polyurethane. Examples of some of the aforesaid are provided in US5958430, US5925552, US5278063 and US5330911 and the contents of the aforementioned specifications are incorporated herein by reference.

In one embodiment, said bio-compatible moieties may comprise bone morphogenic protein (BMP) as described in US4563489 and patents cited therein and the contents of the aforesaid are incorporated herein. Said BMP may be provided in combination, for example in admixture, with a physiologically acceptable biodegradable organic polymer and said biodegradable polymer may be associated with said at least two moieties of said polymer of said bio-compatible polymeric material, for example by being

covalently bonded to said at least two moieties. Thus, in this case, the combination of said biodegradable polymer and BMP defines said bio-compatible moieties. Said biodegradable polymer is preferably a biodegradable polylactic acid; or alternatively, other physiologically acceptable biodegradable organic polymers which are structurally equivalent to polylactic acid can be used as the delivery system for BMP. Examples include poly(hydroxy organic carboxylic acids) e.g. poly(hydroxy aliphatic carboxylic acids), polyglycollic acid, polyglactin, polyglactic acid and poly adonic acids.

In another embodiment, said bio-compatible moieties may be selected from inorganic crystalline structures, inorganic amorphous structures, organic crystalline structures and organic amorphous structures. Preferred bio-compatible moieties are phosphorous based ceramics, for example calcium-phosphorous ceramics. Phosphates in general are suitable but calcium phosphates and calcium apatite are preferred. Especially preferred is hydroxyapatite, a synthetic Ca-P ceramic.

Whilst said bio-compatible moieties may be associated by any suitable means with the functionalised polymer, for example by covalent bond(s), hydrogen bond(s), encapsulation in a matrix which is bonded to or otherwise interacts with said functionalised groups, or by ionic interaction(s), it is preferred that there are covalent bonds between the bio-compatible moieties and said polymer or there are ionic interactions between said bio-compatible moieties and said polymer.

Thus, the invention extends to a method of making a bio-compatible polymeric material for use in medical applications, the method including associating bio-compatible moieties with a functionalised polymer of a type, or when prepared as described, according to said first aspect.

Unless otherwise stated in this specification, a phenyl moiety may have 1,4- or 1,3-, especially 1,4-, linkages to moieties to which it is bonded.

Said polymer may include more than one different type of repeat unit of formula I; more than one different type of repeat unit of formula II; and more than one different type of repeat unit of formula III. Preferably, however, only one type of repeat unit of formula I, II and/or III is provided.

Said moieties I, II and III are suitably repeat units. In the polymer, units I, II and/or III are suitably bonded to one another - that is, with no other atoms or groups being bonded between units I, II, and III.

Where the phenyl moieties in units I, II or III are optionally substituted (prior to any functionalisation in stage (1) of the method), they may be optionally substituted by one or more halogen, especially fluorine and chlorine, atoms or alkyl, cycloalkyl or phenyl groups. Preferred alkyl groups are C_{1-10}, especially C_{1-4}, alkyl groups. Preferred cycloalkyl groups include cyclohexyl and multicyclic groups, for example adamantyl.

Another group of optional substituents of the phenyl moieties in units I, II or III (prior to any functionalisation in stage (1) of said method) include alkyls, halogens, C_yF_{2y+1} where y is an integer greater than zero, O-R^q (where R^q is selected from the group consisting of alkyls, perfluoralkyls and aryls), $CF=CF_2$, CN, NO_2 and OH. Trifluormethylated phenyl moieties may be preferred in some circumstances.

Preferably, said phenyl moieties are not optionally-substituted (prior to any functionalisation in stage (1) of said method).

Where said polymer is cross-linked, it is suitably cross-linked so as to improve its properties. Any suitable means may be used to effect cross-linking. For example, where E represents a sulphur atom, cross-linking between polymer chains may be effected via sulphur atoms on respective chains. Preferably, said polymer is not optionally cross-linked as described.

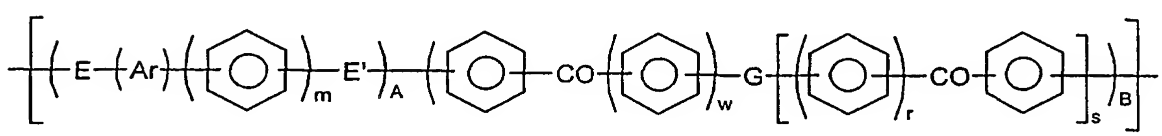
Where w and/or z is/are greater than zero, the respective phenylene moieties may independently have 1,4- or 1,3-linkages to the other moieties in the repeat units of formulae II and/or III. Preferably, said phenylene moieties have 1,4- linkages.

Preferably, the polymeric chain of the polymer does not include a -S- moiety. Preferably, G represents a direct link.

Suitably, "a" represents the mole % of units of formula I in said polymer, suitably wherein each unit I is the

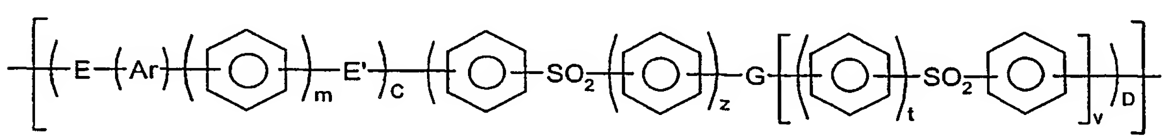
same; "b" represents the mole % of units of formula II in said polymer, suitably wherein each unit II is the same; and "c" represents the mole % of units of formula III in said polymer, suitably wherein each unit III is the same. Preferably, a is in the range 45-100, more preferably in the range 45-55, especially in the range 48-52. Preferably, the sum of b and c is in the range 0-55, more preferably in the range 45-55, especially in the range 48-52. Preferably, the ratio of a to the sum of b and c is in the range 0.9 to 1.1 and, more preferably, is about 1. Suitably, the sum of a, b and c is at least 90, preferably at least 95, more preferably at least 99, especially about 100. Preferably, said polymer consists essentially of moieties I, II and/or III.

Said polymer may be a homopolymer having a repeat unit of general formula



IV

or a homopolymer having a repeat unit of general formula

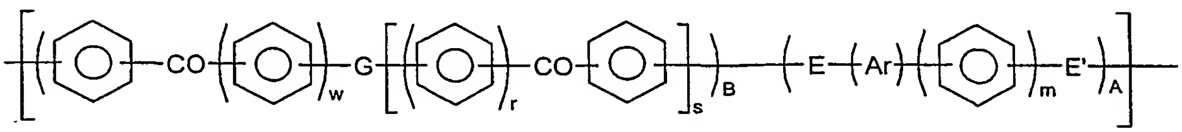


V

or a random or block copolymer of at least two different units of IV and/or V

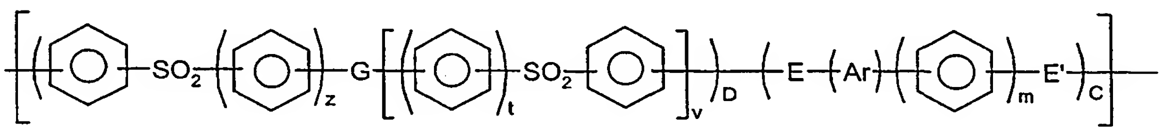
wherein A, B, C and D independently represent 0 or 1 and E,E',G,Ar,m,r,s,t,v,w and z are as described in any statement herein.

As an alternative to a polymer comprising units IV and/or V discussed above, said polymer may be a homopolymer having a repeat unit of general formula



IV*

or a homopolymer having a repeat unit of general formula



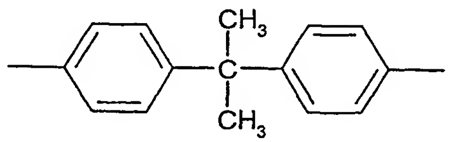
V*

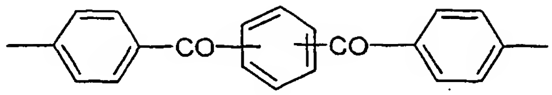
or a random or block copolymer of at least two different units of IV* and/or V*, wherein A, B, C, and D independently represent 0 or 1 and E, E', G, Ar, m, r, s, t, v, w and z are as described in any statement herein.

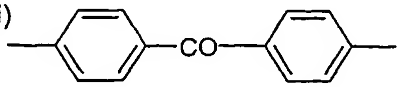
Preferably, m is in the range 0-3, more preferably 0-2, especially 0-1. Preferably, r is in the range 0-3, more preferably 0-2, especially 0-1. Preferably t is in the range 0-3, more preferably 0-2, especially 0-1. Preferably, s is 0 or 1. Preferably v is 0 or 1. Preferably, w is 0 or 1. Preferably z is 0 or 1.

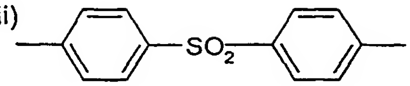
Preferably, said polymer is a homopolymer having a repeat unit of general formula IV.

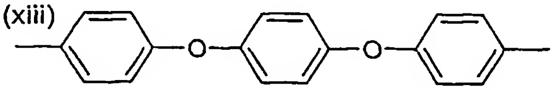
Preferably Ar is selected from the following moieties (xi)*, (xi)**,(xi) to (xxi):

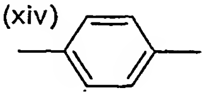
(xi)** 

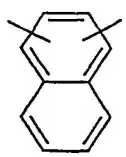
(xi)* 

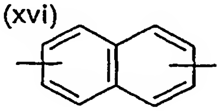
(xi) 

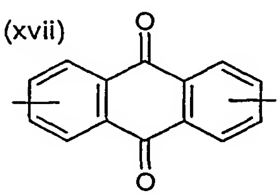
(xii) 

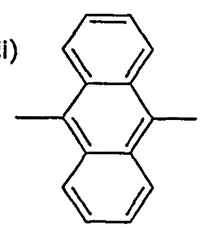
(xiii) 

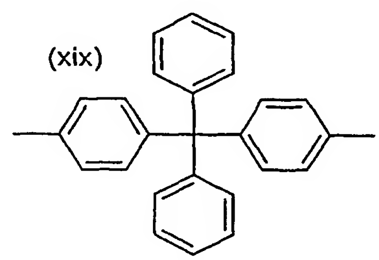
(xiv) 

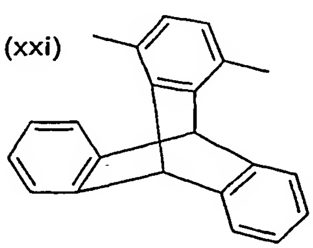
(xv) 

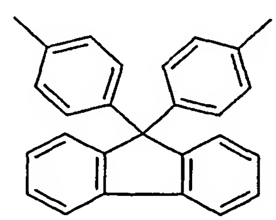
(xvi) 

(xvii) 

(xviii) 

(xix) 

(xxi) 

(xx) 

In (xi)*, the middle phenyl may be 1,4- or 1,3-substituted.

Preferably, (xv) is selected from a 1,2-, 1,3-, or a 1,5- moiety; (xvi) is selected from a 1,6-, 2,3-, 2,6- or a 2,7- moiety; and (xvii) is selected from a 1,2-, 1,4-, 1,5-, 1,8- or a 2,6- moiety.

One preferred class of polymers does not include any moieties of formula III, but suitably only includes moieties of formulae I and/or II. Where said polymer is a homopolymer or random or block copolymer as described, said homopolymer or copolymer suitably includes a repeat unit of general formula IV. Such a polymer may, in some embodiments, not include any repeat unit of general formula V.

Suitable moieties Ar are moieties (i)*, (i), (ii), (iii) and (iv) and, of these, moieties (i)*, (i) and (iv) are preferred. Other preferred moieties Ar are moieties (xi)*, (xii), (xi), (xiii) and (xiv) and, of these, moieties (xi)*, (xi) and (xiv) are especially preferred.

An especially preferred class of polymers are polymers which consist essentially of phenyl moieties in conjunction with ketone and/or ether moieties. That is, in the preferred class, the polymer does not include repeat units which include -S-, $-SO_2-$ or aromatic groups other than phenyl. Preferred polymers of the type described include:

(a) a polymer consisting essentially of units of formula IV wherein Ar represents moiety (iv), E and E' represent oxygen atoms, m represents 0, w represents 1, G represents a direct link, s represents 0, and A and B represent 1 (i.e. polyetheretherketone).

(b) a polymer consisting essentially of units of formula IV wherein E represents an oxygen atom, E' represents a direct link, Ar represents a moiety of structure (i), m represents 0, A represents 1, B represents 0 (i.e.polyetherketone);

(c) a polymer consisting essentially of units of formula IV wherein E represents an oxygen atom, Ar represents moiety (i)*, m represents 0, E' represents a direct link, A represents 1, B represents 0, (i.e. polyetherketoneketone).

(d) a polymer consisting essentially of units of formula IV wherein Ar represents moiety (i), E and E' represent oxygen atoms, G represents a direct link, m represents 0, w represents 1, r represents 0, s represents 1 and A and B represent 1. (i.e.polyetherketoneetherketoneketone).

(e) a polymer consisting essentially of units of formula IV, wherein Ar represents moiety (iv), E and E' represents oxygen atoms, G represents a direct link, m represents 0, w represents 0, s, r, A and B represent 1 (i.e. polyetheretherketoneketone).

Of the aforesaid, the polymers described in (a) and (b) are preferred, with the polymer described in (a) being especially preferred.

Preferably, the method involves functionalising the polymer at or adjacent a surface thereof, such that the

bulk of the polymer is not substantially functionalised. Thus, the method preferably involves functionalising aryl moieties of said polymer such that the concentration of non-functionalised aryl moieties (i.e. aryl moieties not functionalised in the method) present within the bulk of the functionalised polymer is greater than the concentration of non-functionalised aryl moieties present at or adjacent the surface. Also, the concentration of bio-compatible moieties in the bulk is suitably less than present at the surface.

Preferably, said polymer functionalised in the method is presented as a solid, suitably shaped so as to represent at least part of a device for use in medical applications, and then functionalised in the method. For example, said device may be a component of an implant for a human or animal body, for example an orthopaedic or dental implant or vascular graft. Said solid may be provided in a desired shape by any suitable means, for example by injection or compression moulding or by film formation techniques or extrusion. Thus, preferably, stages (1) and (2) of said method according to said first aspect are undertaken on said polymer in solid form, suitably so as to preferentially functionalise a surface region of said solid and associate bio-compatible moieties therewith.

The method preferably includes the step of treating said polymer after functionalisation of said aryl moieties in stage (1) with a material for providing bio-compatible moieties (hereinafter "BCM material"). Said BCM material may be arranged to provide any of the bio-compatible moieties described hereinafter. Said polymer may be

provided as a solid. Suitably, said bio-compatible moieties are caused to become associated with a surface of said solid, preferably with functional groups pendent from functionalised aryl moieties at a surface of said solid. Said solid is preferably shaped so as to represent at least a part of a device for use in medical applications, as described above. Preferably, after association with said bio-compatible moieties, the bio-compatible material formed (referred to as "bio-compatible polymeric material") is not engineered or otherwise treated in a manner which may result in substantial depletion of the bio-compatible moieties associated with its surface.

Stage (1) preferably involves subjecting said polymer to an electrophilic aromatic substitution reaction. The identity of the polymer, the identity of the electrophile and the conditions of the treatment may be selected to control the extent of electrophilic substitution (both in terms of the aryl moieties of said polymer which are substituted and the depth of substitution). For example, it is found that the ease of electrophilic aromatic substitution on a particular phenyl moiety in a polymer of the types described is dependent upon the identity of groups to which the phenyl moiety is bonded. The more electron withdrawing the groups bonded to a phenyl moiety, the less susceptible the group is to electrophilic aromatic substitution. Thus, taking polyarylether ketones as an example, the ease of electrophilic aromatic substitution decreases down the following list, wherein Ph represents a phenyl group:

-O-Ph-Ph-O

-O-Ph-O-.

-O-Ph-CO-

-CO-Ph-CO-

Polymers which include sulphone and/or thioether moieties may behave in a similar fashion. Compared to polyaryletherketones, -S-Ph-Ph-S- and -S-Ph-S- may be substitutable with about the same ease as for the ether equivalents. However, sulphone containing moieties may render phenyl groups less easy to sulphonate compared to the ketone equivalents. Thus, by careful selection of the polymers and the conditions for electrophilic aromatic substitution, the electrophilic substitution can be carefully controlled and, consequently, the concentration and spacial distribution of sites where bio-compatible moieties may be associated with the polymer can be controlled. Thus, the method may be advantageously used to optimise the concentration and spacial distribution of bio-compatible moieties at or adjacent the surface of the polymer.

Preferably, no $-CO(Ph)_n-CO-$ or $-SO_2-(Ph)_n-SO_2-$ moieties, where n is an integer, are substituted by an electrophile in the method. Preferably, no $-CO-(Ph)_n-O-$, $-CO(Ph)_n-S-$, $-SO_2-(Ph)_n-O-$ or $-SO_2-(Ph)_n-S-$ moieties are substituted by an electophile in the method.

The method may involve treating the polymer with any known reagent(s) arranged for electrophilic aromatic substitution. Preferred electrophilic aromatic substitution reactions include sulphonation, chlorosulphonation, nitration, acylation, halogenation, chloromethylation, phosphonylation, lithiation and (optionally-substituted)alkylation reactions. Of the

aforesaid, halogenation may be least preferred. Preferred reactions involve contact of the polymer with a liquid.

Sulphonation may result in an $-SO_3H$ group being introduced onto an aryl, especially a phenyl moiety. Preferably, a sulphonic acid, especially chlorosulphonic acid is used in the method. Chlorosulphonation may involve a sulphonation reaction as described followed by chlorination of the sulphonate unit, for example using thionyl chloride or any other suitable chlorinating agent. Nitration may be effected using a nitric acid/sulphuric acid mixture. Preferably, the mixture is selected so that any competing sulphonation is suppressed thereby leading to nitration only. Acylation may be effected by a Friedel-Crafts reaction, for example using a reagent which includes a ketone group and aluminium chloride. For example, a compound $R^{20}COCl$ may be used to introduce a moiety $R^{20}CO-$ wherein R^{20} represents an optionally-substituted alkyl or aryl group. In another example, a cyclic anhydride (e.g. of formula $CH_2CH_2CH_2CO.O.CO$ – glutaric anhydride) may be used thereby to introduce a moiety $-CO-(CH_2)_n-COOH$ wherein n is an integer. (Optionally-substituted) alkylation may result in the introduction of a group $R^{21}-R^{22}-$ wherein R^{22} represents an alkyl or alkenyl moiety, especially an alkyl moiety, and R^{21} represents a functional group, suitably selected from a halogen, especially a chlorine, atom (in which case $R^{21}-R^{22}-$ may represent a chloroalkyl, especially a chloromethyl group) and a sulphonate group. Where R^{21} represents a sulphonate group, a cyclic compound which includes a $-SO_2-O-$ moiety in its ring, for example a sultone, may be used in the reaction.

Control of the electrophilic aromatic substitution reactions (so as to substitute selected parts of the polymer and/or to substitute the polymer to a particular depth) may involve selecting particular concentrations of electrophilic reagents. Thin surface modifications may be preferred, for example to a depth of less than 50, preferably less than 30, more preferably less than 20, especially 10 Angstroms or less. A depth of 3-10 Angstroms may be preferred.

In preferred embodiments, the solvent in which functionalisation is undertaken may be selected such that the polymer has low or substantially no solubility in the solvent.

Preferably, the electrophilic aromatic substitution reaction is undertaken for a predetermined time. Preferably, after said predetermined time, steps are taken to stop the reactions, for example by removal of the polymer and/or by washing.

In some cases, reagents may be selected whereby multiple functionalisation of aryl moieties of said polymer may take place. Preferably, no more than three, more preferably no more than two, especially only one hydrogen atom of an aryl moiety is substituted in an electrophilic reaction as described.

After said electrophilic aromatic substition reaction,said polymer having functionalised aryl moieties may be associated with bio-compatible moieties as described, without any further treatment of said aryl moieties. However, it may be preferred for said polymer

to be subjected to a further treatment thereby to functionalise the electrophilic moieties introduced in stage (1), preferably to introduce a functional group pendent from the functionalised aryl moieties which can be associated with bio-compatible moieties in stage (2). Thus, functionalised aryl moieties may include functional groups selected from the following for association with bio-compatible moieties: -OH, -CHO, $-NR^{10}_2$, preferably $-NH_2$ or $-NHR^{10}$, -SH, $-CONH_2$, $-CONHR^{10}$, -COOH, -COCl or $-COOR^{10}$ group, a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, $-NO_2$, $-SO_3M$, $-SO_2R^{11}$, $-SO_2NHR^{10}$, $-SO_2NR^{10}_2$ or -COOM groups, an anhydride, an epoxide, a cyanate, -CN, an isocyanate, a carbon-carbon double bond, for example a group $-CR^{10}=CR^{10}_2$ or a (C_o-C_{10}alk) acrylate (wherein "alk" refers to an alkyl group) such as $-COOC(CH_3)CH_2$ and $-COOCHCH_2$, a carbon-carbon triple bond, for example a group $-CR^{10}$ or an azide, wherein R^{10} represents a hydrogen atom or an optionally substituted alkyl group, wherein M represents a hydrogen atom or an alkali metal and R^{11} represents a halogen, especially a chlorine, atom.

BCM material described above may include any suitable functional group that is arranged to become associated with functional groups of said functionalised aryl moieties of said polymer and may be selected from any of the functional groups referred to above for said functionalised aryl moieties provided that a selected functional group on said functionalised polymer is capable of becoming associated with, suitably reacting with, a selected functional group provided by BCM material.

In some cases a bio-compatible moiety may be provided by reaction of said functionalised polymer with more than one functional group. For example a bio-compatible moiety may be a polyurethane which may be prepared: when said functionalised polymer provides a hydroxy group and said BCM material provides a diisocyanate and a diol; or when said functionalised polymer provides an isocyanate group and said BCM material provides a diisocyanate and a diol. In both cases, BCM material is suitably provided by use of two different compounds.

In some cases, BCM material may be provided by a monomer or monomers having a functional group arranged to react with said functionalised polymer and being arranged to polymerise to provide a polymeric bio-compatible moiety.

In one embodiment, said functionalised polymer may include ionic functional groups, for example -COOM or $-SO_3M$, and such groups may be arranged to ionically associate with an ionic moiety provided by BCM material.

In other embodiments, an amide bond may be formed between said functionalised polymer and BCM material.

In some cases, said functionalised polymer may be multi-functional, thereby enabling it to associate with a plurality of bio-compatible moieties. For example, multi-functionality may be provided by dendritic or hyperbranched end groups.

Where said polymer is subjected to further treatment(s) thereby to functionalise the electrophilic

moieties introduced in stage (1), such treatment(s) may include reduction reactions (e.g. of nitro groups to amine groups), salt formation (e.g. to form $-SO_3Na$), halogenation (e.g. to form $-SO_2Cl$) or treatment with other linker or spacer moieties. Linker or spacer moieties which may extend between aryl moieties functionalised in stage (1) and bio-compatible moieties introduced in stage (2) may include any suitable linking group and such linking groups may include saturated, unsaturated, linear, branched or cyclic moieties. Preferred linking groups include optionally substituted alkyl, alkenyl, alkynyl, heteroalkyl e.g. -N-alkyl, aryl, heteroaryl, e.g. pyridyl, alkylaryl, hetero(aryl)alkyl, e.g. -O-aryl-alkyl, (hetero) heteroaryl e.g. -N-heteroaryl and (hetero)aryl e.g. -O-aryl.

According to a second aspect, there is provided a bio-compatible polymeric material, wherein the bulk of the material comprises a polymer having a moiety of formula I and/or of formula II and/or formula III as described according to said first aspect, wherein a surface of said material comprises a functionalised derivative of said polymer present in the bulk wherein bio-compatible moieties are associated with functionalised aryl moieties at or adjacent said surface.

Since said functionalised polymeric material is suitably only functionalised at or adjacent its surface and functionalised polymer represents only a small fraction of the total weight of the polymer, the existence of functionalised polymer may have a limited effect on the bulk properties of the polymeric material.

The glass transition temperature (T_g) of said polymer, suitably the bulk thereof, (in the absence of associated bio-compatible moieties) may be at least 135°C, suitably at least 150°C, preferably at least 154°C, more preferably at least 160°C, especially at least 164°C. In some cases, the Tg may be at least 170°C, or at least 190°C or greater than 250°C or even 300°C.

Said polymer, suitably the bulk thereof, (in the absence of associated bio-compatible moieties) may have an inherent viscosity (IV) of at least 0.1, suitably at least 0.3, preferably at least 0.4, more preferably at least 0.6, especially at least 0.7 (which corresponds to a reduced viscosity (RV) of least 0.8) wherein RV is measured at 25°C on a solution of the polymer in concentrated sulphuric acid of density $1.84gcm^{-3}$, said solution containing 1g of polymer per $100cm^{-3}$ of solution. IV is measured at 25°C on a solution of polymer in concentrated sulphuric acid of density $1.84gcm^3$, said solution containing 0.1g of polymer per $100cm^3$ of solution.

The measurements of both RV and IV both suitably employ a viscometer having a solvent flow time of approximately 2 minutes.

The main peak of the melting endotherm (Tm) for said polymer, suitably the bulk thereof, (if crystalline) may be at least 300°C.

Preferably, said polymer, suitably the bulk thereof, (in the absence of associated bio-compatible moieties) has at least some crystallinity or is crystallisable. The existence and/or extent of crystallinity in a polymer is

preferably measured by wide angle X-ray diffraction, for example as described by Blundell and Osborn (Polymer 24, 953, 1983). Alternatively, crystallinity may be assessed by Differential Scanning Calorimetry (DSC).

Said polymer suitably the bulk thereof, (in the absence of associated bio-compatible moieties) may have a number average molecular weight in the range 2000-80000. Preferably said molecular weight is at least 14,000. The molecular weight may be less than 60,000.

Said bio-compatible polymeric material suitably has a tensile strength (according to ISO R527) of at least 80, preferably at least 90, especially at least 95 MPa. The tensile strength may be less than 360, suitably less than 250, preferably less than 140 MPa. It preferably has an elongate at break (according to ISO R527) of at least 40, preferably at least 50%. It preferably has a tensile modulus (according to ISO R527) of greater than 2.5, preferably greater than 3, especially greater than 3.5 GPa. The tensile modulus may be less than 40, suitably less than 30, preferably less than 20, more preferably less than 10 GPa. It preferably has a flexural strength (according to ASTM D695) of at least 100, more preferably at least 110, especially at least 115 MPa. The flexural strength may be less than 650, preferably less than 400, more preferably less than 260, especially less than 200 MPa. It preferably has a flexural modulus (according to ISO R178) of at least 3, preferably at least 3.5, especially at least 4 GPa. The flexural modulus may be less than 60, suitably less than 25, preferably less than 20 especially less than 10 GPa. Advantageously, the aforementioned properties can be adjusted by appropriate

selection of polymers and/or any reinforcement means included in said support material to suit particular applications. For example, a continuous carbon fibre polyetheretherketone may typically have a tensile strength of about 350 MPa, a tensile modulus of 36 GPa, an elongation of 2%, a flexural modulus of SO GPa and a flexural strength of 620 MPa. A polyaryletherketone with 30% of high performance fibres may typically have a tensile strength of 224 MPa, a tensile modulus of 13 GPa, a tensile elongation of 2%, a flexural modulus of 20 GPa and a flexural strength of 250 MPa.

Said bio-compatible polymeric material may include one or more fillers for providing desired properties. Said material preferably incorporates an X-ray contrast medium. Fillers and/or said X-ray contrast medium is/are preferably distributed substantially uniformly throughout said material.

Where an X-ray contrast medium is provided it suitably comprises less than 25wt%, preferably less than 20wt%, more preferably less than 15wt%, especially less than 10wt% of said bio-compatible material. Where it is provided, at least 2wt% may be included. Preferred X-ray contrast mediums are particulate and preferably are inorganic. They preferably have low solubility in body fluids. They preferably also have a sufficient density compared to that of the polymer to create an image if a compounded mixture of the polymer and contrast medium are X-ray imaged. Barium sulphate and zirconium oxide are examples. Said particulate material is suitably physically held in position by entrapment within the polymer.

Preferably, said bio-compatible polymeric material includes a major amount of said polymer having moieties I, II and/or III.

In the context of this specification, a "major" amount may mean greater than 50 wt%, suitably greater than 65 wt%, preferably greater than 80 wt%, more preferably greater than 95 wt%, especially greater than 98 wt% of the referenced material is present relative to the total weight of relevant material present.

Said bio-compatible polymeric material may comprise a blend which includes at least two polymers of a type described according to said first aspect. For example, said at least two polymers preferably include moieties I, II and/or III as described above. A said blend preferably includes a major amount of higher (or the highest) number average molecular weight polymer. Said functionalised and/or bio-compatible polymeric material preferably includes a major amount of a higher molecular weight polymer.

Preferably, said bio-compatible moieties are associated with moieties which are pendent from aryl moieties of the polymer at or adjacent the surface thereof.

Polymers of the type described may be prepared as described in PCT/GB99/02833.

According to a third aspect of the present invention, there is provided a device for use in medical applications, wherein said device comprises a bio-

compatible polymeric material according to said second aspect or made in a method according to said first aspect or as described in any invention described herein.

Said device is preferably a prosthetic device, for example an implant such as an orthopaedic, dental or maxillofacial implant or a component thereof; or a device, for example a catheter, which is arranged to be temporarily associated with a human or animal body. Said device is preferably a prosthetic device as described. An orthopaedic device may be an implant for a body joint, for example a knee or hip joint or spine fusion device.

A said device may include a part or parts made out of said bio-compatible polymeric material and a part or parts made out of other materials. Suitably, however, said device includes at least 50wt%, preferably at least 65wt%, more preferably at least 80wt%, especially at least 95wt% of said bio-compatible polymeric material. In some embodiments said device may consist essential of said bio-compatible polymeric material.

According to a fourth aspect of the invention, there is provided a method of making a device according to the third aspect, the method comprising: forming a material into a shape which represents or is a precursor of a device or part of a device for use in medical applications wherein said material comprises a polymer having moieties I, II and/or III as described herein; and functionalising said polymer as described according to said first aspect.

The invention extends to the use of a polymer functionalised as described according to said first or

said second aspects in the manufacture of a device for use in a medical treatment, for example in surgery.

Any feature of any aspect of any invention or embodiment described herein may be combined with any feature of any aspect of any other invention or embodiment described herein.

Specific embodiments of the invention will now be described by way of example.

PEEK (Trade Mark) referred to hereinafter is a polyetheretherketone obtained from Victrex Plc.

All chemicals referred to were used as received from Sigma-Aldrich Chemical Company, Dorset, U.K., unless otherwise stated.

All PEEK™ films used were approximately 120μm thick. Film samples were prepared from samples of Victrex PEEK™ (Melt Viscosity 0.45 kNgm^{-2}, at 1000 sec^{-1} at 400°C) powder which was compression moulded between metal plates using a Moore laboratory hot press at 400°C for 5 to 10 minutes. The PEEK™ melt was quenched in ice-cold water in order to obtain 120μm thick amorphous samples. The film samples were refluxed in acetone for 72 hours prior to use.

Example 1 Controlled sulphonation of PEEK™

A sample of PEEK™ film (1cm x 5cm) was placed in a boiling tube under a nitrogen atmosphere. The film was then immersed in a 0.3% v/v solution of chlorosulphonic acid in 1,2-dichloroethane. After approximately 5 minutes the

film was removed from the solution and quenched with distilled water, resulting in the film changing from an orange to a white colour. The film was washed with distilled water, followed by acetone, before being oven dried (40°C) overnight. The film surface was analysed by x-ray photoelectron spectroscopy which indicated that one sulphonic acid group was present for every -O-Ph-O- ring, on the outermost 1-2nm of the films surface.

Example 2 Controlled Nitration and subsequent reduction of PEEK™ film

A sample of PEEK™ film was immersed in 50ml of nitrobenzene to which 2.5 ml of a one part by volume nitric acid (SG = 1.42) and 2 parts by volume sulphuric acid (SG = 1.84) solution was added dropwise. The reactive solution was stirred for 5 minutes before being removed and washed with distilled water.

Sodium dithionite (6.0g, 34.5mmol) was added to 100 ml of DMF and the contents stirred for 30 minutes. The nitrated PEEK™ film was then immersed in the reactive solution and the mixture stirred at reflux for 6 hours. The film sample was then removed and washed with methanol, 2M NaOH solution followed by methanol again, before being dried at room temperature overnight.

Example 3 Calcium Phosphate Deposition on a modified PEEK™ sample from example 1.

A supersaturated calcium phosphate solution containing 5mM $CaCl_2$, 1.5mM KH_2PO_4 and 1.5mM Na2HPO4 was prepared by mixing 1.5ml of 0.1M Na2HPO4 stock solution into 92ml of

deionised water, followed by the slow addition of 5.0ml of 0.1M CaCl2 solution. The combined solution was stirred for 3 minutes and modified PEEK™ film from example 1 was immersed in the solution and taken out just before the solution precipitated (1 hour). The films were then rinsed with deionised water and blown dry with nitrogen. The process can be repeated several times to achieve a desired thickness.

Example 4 Reaction of surface modified PEEK™ containing amino groups with the peptide GRGDS

The modified PEEK™ sample from example 2 was placed in a 250ml round-bottomed flask fitted with a magnetic follower and a nitrogen inlet and outlet and containing N,N-dimethylacetamide (60ml), and disuccinimidylsuberate (300mg). The contents were stirred under an atmosphere of nitrogen at room temperature for 2hrs. The specimen was removed, washed with ether and dried in vacuo for 10hrs at 50°C. The dried sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS(160mg) in an aqueous buffer solution (40ml), pH 9. The functionalised PEEK™ was washed successively with the buffer solution and ether.

Example 5 Friedel Crafts acylation of PEEK™ film

The modified PEEK™ sample from Example 1 was placed in a 700ml flanged flask fitted with a reflux condenser, magnetic follower and a nitrogen inlet and outlet and charged with thionyl chloride (250ml). and dimethylformamide (30ml). Under a nitrogen atmosphere and with continuous stirring the mixture was heated to reflux

for 15 hours. The reaction mixture was allowed to cool to room temperature, the sample was then removed and washed with ether and dried in vacuo.

The dried sample was then placed in a 100ml Schlenk flask and the flask placed under a nitrogen atmosphere. A 5% w/v solution of *p*-aminobenzoic acid solution in acetic acid (50ml) was added to the flask and the reaction mixture stirred at room temperature for 72h. The film was removed and washed with acetic acid followed by distilled water and acetone, before being dried at room temperature overnight.

Example 6 Reaction of surface modified PEEK™ containing carboxylic acid groups with the peptide GRGDS

The surface modified PEEK™ from Example 5 was stirred at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (0.4g) dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino)ethanesulphonic acid) (40ml). The sample of PEEK™ was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS(160mg) in phosphate-buffered saline solution (40ml) (Na_2HPO_4, 1.15g; KH_2PO_4, 0.2g; NaCl. 8g; KCl, 0.2g; $MgCl_2$, 0.1g; $CaCl_2$. 0.1g in 1 Litre of distilled water). The functionalised PEEK™ was washed successively with phosphate buffer and distilled water.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

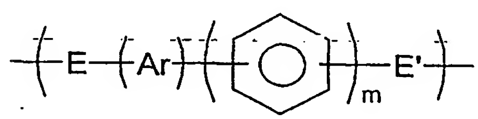
Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

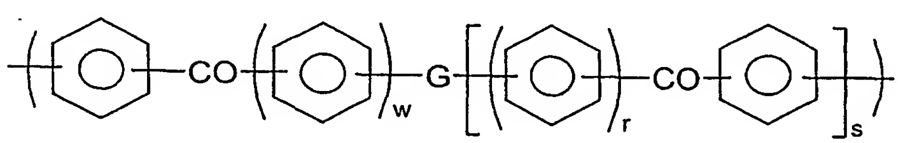
1. A method of functionalising a polymer to produce a bio-compatible polymeric material which includes bio-compatible moieties and is for use in medical applications, the method including the stages of:

(1) treating a polymer which has a moiety of formula



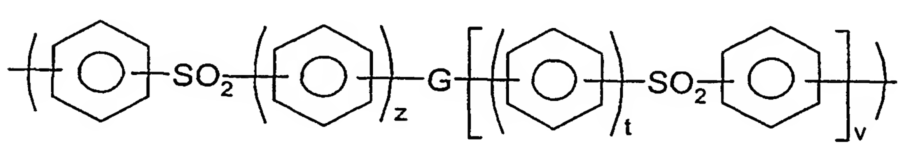
I

and/or a moiety of formula



II

and/or a moiety of formula

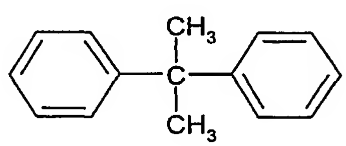


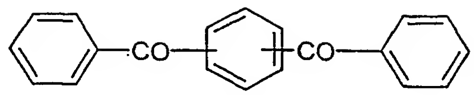
III

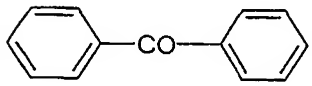
to functionalise aryl, especially phenyl, moieties in said polymer (hereinafter referred to as "functionalised aryl moieties") at or adjacent a surface of the polymer whilst

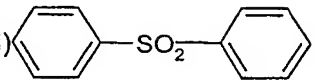
not functionalising corresponding aryl moieties in the bulk of said polymer, wherein the phenyl moieties in units I, II, and III (prior to functionalisation) are independently optionally substituted and optionally cross-linked; and wherein m,r,s,t,v,w and z independently represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)* (i)**, (i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties

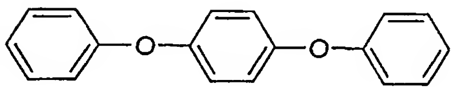
(i)**

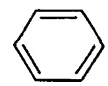


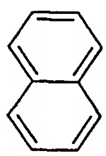
(i)* 

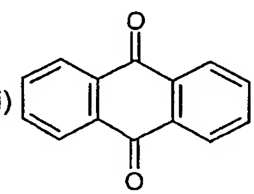
(i) 

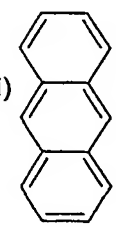
(ii) 

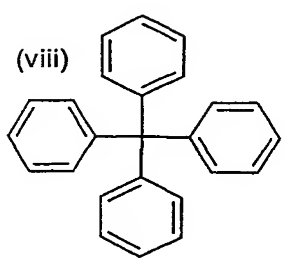
(iii) 

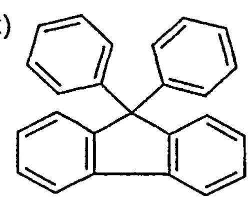
(iv) 

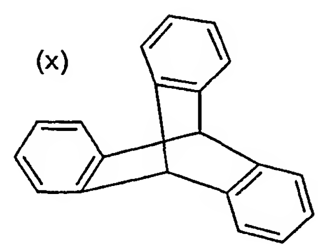
(v) 

(vi) 

(vii) 

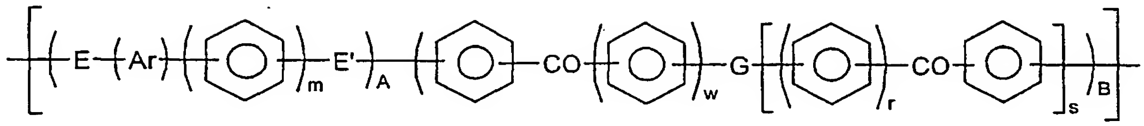
(viii) 

(ix) 

(x) 

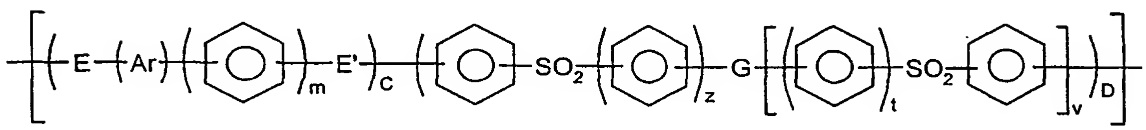
(2) associating bio-compatible moieties with said functionalised aryl moieties so that said bio-compatible moieties are at or adjacent the surface of the polymer.

2. A method according to claim 1, wherein said polymer is a homopolymer having a repeat unit of general formula



IV

or a homopolymer having a repeat unit of general formula

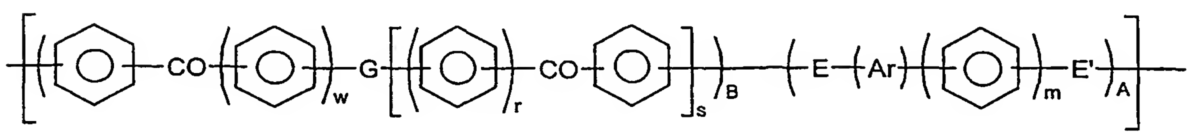


V.

or a random or block copolymer of at least two different units of IV and/or V

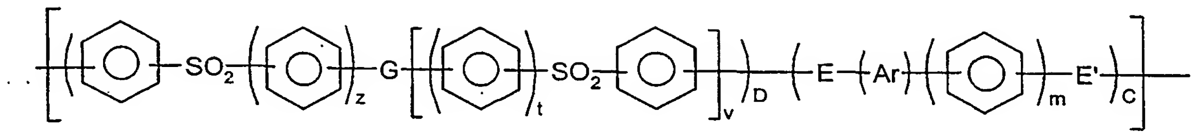
wherein A, B, C and D independently represent 0 or 1 and E,E',G,Ar,m,r,s,t,v,w and z are as described in claim 1; or

said polymer is a homopolymer having a repeat unit of general formula



IV*

or a homopolymer having a repeat unit of general formula



V*

or a random or block copolymer of at least two different units of IV* and/or V*, wherein A, B, C, and D independently represent 0 or 1 and E, E', G, Ar, m, r, s, t, v, w and z are as described in claim 1.

3. A method according to claim 1 or claim 2, wherein said polymer is selected from polyetheretherketone, polyetherketone, polyetherketoneketone, polyetherketoneetherketoneketone and polyetheretherketoneketone.

4. A method according to any preceding claim, wherein said polymer is polyetheretherketone.

5. A method according to any preceding claim, wherein said polymer functionalised in the method is presented as a solid and then functionalised.

6. A method according to any preceding claim, which includes the step of treating said polymer after functionalisation of said aryl moieties in stage (1) with a material for providing bio-compatible moieties.

7. A method according to any preceding claim, wherein stage (1) involves subjecting said polymer to an electrophilic aromatic substitution reaction.

8. A method according to any preceding claim, wherein, no $-CO(Ph)_n-CO-$ or $-SO_2-(Ph)_n-SO_2-$ moieties, where n is an integer, are substituted by an electrophile in the method.

9. A method according to any preceding claim, wherein, no $-CO-(Ph)_n-O-$, $-CO(Ph)_n-S-$, $-SO_2-(Ph)_n-O-$ or $-SO_2-(Ph)_n-S-$ moieties are substituted by an electrophile in the method.

10. A method according to any preceding claim, wherein said polymer is treated to undergo an electrophilic aromatic substitution reaction selected from sulphonation, chlorosulphonation, nitration, acylation, halogenation, chloromethylation, phosphonylation, lithiation and (optionally-substituted) alkylation reactions.

11. A method according to any preceding claim, wherein said polymer is treated to undergo a thin surface modification to a depth of less than 100 Angstroms.

12. A method according to any preceding claim, wherein said treatment of said polymer involves an electrophilic aromatic substitution reaction for a predetermined time wherein, after said predetermined time, steps are taken to stop the reaction.

13. A method according to any preceding claim, wherein after said treatment described in stage (1), said polymer is subjected to a further treatment thereby to functionalise electrophilic moieties introduced in stage (1), thereby to introduce a functional group pendent from the functionalised aryl moieties which can be associated with bio-compatible moieties in stage (2).

14. A method according to claim 13, wherein said functional groups pendent from the functionalised aryl moieties are selected from -OH, -CHO, $-NR^{10}_2$, -SH, $-CONH_2$, $-CONHR^{10}$, -COOH, -COCl and $-COOR^{10}$ groups, a halogen atom, $-NO_2$, $-SO_3M$, $-SO_2R^{11}$, $-SO_2NHR^{10}$, $-SO_2NR^{10}_2$ and -COOM groups, an anhydride, an epoxide, a cyanate, -CN, an isocyanate, a carbon-carbon double bond, a carbon-carbon triple bond and an azide, wherein R^{10} represents a hydrogen atom or an optionally substituted alkyl group, wherein M represents a hydrogen atom or an alkali metal and R^{11} represents a halogen atoms.

15.A bio-compatible polymeric material, wherein the bulk of the material comprises a polymer having a moiety of formula I and/or of formula II and/or of formula III as described in claim 1, wherein a surface of said material comprises a functionalised derivative of said polymer present in the bulk wherein bio-compatible moieties are associated with functionalised aryl moieties at or adjacent said surface.

16.A bio-compatible polymeric material according to claim 15, said material incorporating an X-ray contrast medium.

17.A device for use in medical applications, wherein said device comprises a bio-compatible polymeric material according to claim 15 or claim 16 or made in the method according to any of claims 1 to 14.

18.A method of making a device according to claim 17, the method comprising: forming a material into a shape which represents or is a precursor of a device or part of a device for use in medical applications wherein said

material comprises a polymer having moieties I, II and/or III as described in claim 1; and functionalising said polymer as described in any of claims 1 to 14.

19. The use of a polymer functionalised as described in any of claims 1 to 14 or a bio-compatible polymeric material as described in claim 15 or claim 16 in the manufacture of a device for use in a medical treatment.

INTERNATIONAL SEARCH REPORT

Inte[redacted]onal Application No
PCT/GB 01/02818

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/14 C08G65/48 C08J7/12 A61L31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F A61M C08L C08G C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, COMPENDEX, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARCHAND-BRYNAERT J ET AL: "Surface fluorination of PEEK film by selective wet-chemistry" POLYMER, ELSEVIER SCIENCE PUBLISHERS B.V, GB, vol. 38, no. 6, 1 March 1997 (1997-03-01), pages 1387-1394, XP004055782 ISSN: 0032-3861 page 1392, right-hand column -page 1393, left-hand column --- -/--	1-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2001	16/11/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Muñoz, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	NOISET OLIVIER ET AL: "Surface modification of poly(aryl ether ether ketone) (PEEK) film by covalent coupling of amines and amino acids through a spacer arm" J POLYM SCI PART A;JOURNAL OF POLYMER SCIENCE, PART A: POLYMER CHEMISTRY DEC 1997 JOHN WILEY & SONS INC, NEW YORK, NY, USA, vol. 35, no. 17, December 1997 (1997-12), pages 3779-3790, XP002180806 page 3788 ---	1-19
X	HENNEUSE C ET AL: "Surface carboxylation of PEEK film by selective wet-chemistry" POLYMER, ELSEVIER SCIENCE PUBLISHERS B.V, GB, vol. 39, no. 4, 1 February 1998 (1998-02-01), pages 835-844, XP004099267 ISSN: 0032-3861 the whole document ---	1-19
X	NOISET OLIVIER ET AL: "Fibronectin adsorption or/and covalent grafting on chemically modified PEEK film surfaces." JOURNAL OF BIOMATERIALS SCIENCE POLYMER EDITION, vol. 10, no. 6, 1999, pages 657-677, XP001034344 ISSN: 0920-5063 abstract ---	1-19
A	J. ROOVERS; FEI WANG: "Poly(Aryl Ether Ketone): Functionalization" SALAMONE J.C. (ED); POLYMERIC MATERIALS ENCYCLOPEDIA, CRC PRESS, BOCA RATON, FL, USA, vol. 7, 1996, pages 5527-5532, XP002181431 the whole document ---	1-19
A	BREITBACH L ET AL.: "heterogeneous functionalizing of polysulfone membranes" DIE ANGEWANDTE MAKROMOLECÜLARE CHEMIE, vol. 184, 1991, pages 183-196, XP002180807 the whole document ---	1-19
T	EP 1 099 468 A (INST DEUTSCHE) 16 May 2001 (2001-05-16) the whole document -----	1-19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,2,5-19 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the polyetherketones of claims 3 and 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted]onal Application No

PCT/GB 01/02818

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1099468 A	16-05-2001	DE 19954158 A1	17-05-2001
		EP 1099468 A2	16-05-2001
		JP 2001200089 A	24-07-2001